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BRIEF COMMUNICATION

A simple bone cyst of the distal humerus with a t(7;12)(q21;q24.3) in a patient with hypophosphatemic rickets

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Few studies describe karyotypic abnormalities in simple bone cysts. We report the results of cytogenetic analysis of a case of simple bone cyst of the distal humerus in a patient with hypophosphatemic rickets with a t(7;12)(q21;q24.3) as the sole abnormality. To our knowledge, this is the third report of a cytogenetically characterized tumor of this type.

Keywords Cytogenetic, bone, cyst, hypophosphatemic rickets, t(7;12)

A simple bone cyst (SBC) is defined as an intramedullary, usually unilocular, bone cyst (cavity) filled with serous or serosanguineous fluid. A SBC can produce pain and swelling, but more frequently, patients present after a pathological fracture. Males predominate in a ratio of 3:1. About 85% of patients are in the first two decades of life. Recurrence is reported in 10–20% of cases, especially those involving children (1). Cytogenetic studies of SBCs are extremely limited. Only two reports on cytogenetic analysis of this tumor type have been published. One case, reported by Vayego et al. (2), involved an 11-year-old boy whose tumor demonstrated a complex clonal rearrangement involving chromosomes 4, 6, 8, 16, and 21 and both chromosome 12 homologues. This patient had four recurrences; the fourth recurrence was examined and was found to be positive for a *TP53* mutation. A transition C>T and a transversion G>C in codons 248 and 249 resulted in the substitution of the amino acids arginine for tryptophan and arginine for serine, respectively (3). The second case, described by Richkind et al. (4), involved a 9-year-old boy whose tumor presented with a t(16;20)(p11.2;q13) as the sole cytogenetic abnormality.

Materials and methods

The patient, a 13-year-old girl, presented with progressive subacute musculoskeletal pain and asthenia that had begun 3 years prior. She lost the ability to walk 1 year after the onset of symptoms. Her parents were second cousins, and there was no history of affected relatives. A simple radiological work up showed diffuse osteopenia and progressive skeletal deformities. Biochemical tests disclosed hypophosphatemia, elevated alkaline phosphatase and parathyroid hormone. The first suspected diagnosis was oncogenic osteomalacia; however, no mesenchymal tumor was identified. The patient started treatment with oral calcitriol and phosphorus. During the investigation for the metabolic condition, a lesion in her right humerus was discovered and biopsied. Image studies revealed a unicameral cystic lesion affecting the distal two thirds of the left humerus (Figures 1A and 1B). A histological examination of the curetted material of the internal cyst wall revealed a predominantly thin connective tissue membrane with an inconspicuous cellular lining; in some more thick areas, cholesterol crystal clefts, collections of foamy histiocytes, and hemosiderin pigment were seen (Figures 1C and 1D). Taken together, image and histological findings were consistent with the diagnosis of SBC.

Cytogenetic analysis

For cytogenetic studies, a representative tissue fragment of the right humerus lesion was mechanically disaggregated with a caliper and scalpel. The tissue fragments were used to initiate an explant culture. The small fragments were distributed in a 25 cm^2 T-flask inverted after seeding and incubated overnight with McCoy's 5A medium supplemented with L-glutamine, antibiotics and 20% fetal bovine serum at 37°C and 5% carbon dioxide. Thereafter, the flask was gently

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turned so that the tissue fragments were covered with the medium. Chromosome preparation was performed after 12 days of primary culture when the cells were spindle shaped and revealed a monolayer growth pattern in the inverted microscope. The chromosomes were prepared according to previously published methods (5). Wright stain was used for trypsin Giemsa-banding (G-banding). At least 20 metaphases were analyzed, and chromosome aberrations were classified according to the International System for Human Cytogenetic Nomenclature (ISCN 2009) (6).

Results

The G-banding analysis revealed that five of 20 metaphase cells examined from the primary culture had an abnormal clone characterized by a t(7;12)(q21;q24.3). Of the remaining cells, 14 had a normal chromosome complement. One cell had a nonclonal change. The karyotype was interpreted as 46,XX,t(7;12)(q21;q24.3)[5] (Figure 1E). These particular rearrangements have been described neither in benign lesions nor in malignant bone tumors.

Discussion

SBCs are nonneoplastic lesions, classified among tumors of undefined neoplastic nature in the *World Health Organization Classification of Tumours*, that often constitute important lesions to be considered in the differential diagnosis of bone tumors (7). Recurrence of SBC is reported at 10−20% of cases, especially in children (1). Growth arrest of the affected bone and avascular necrosis of the head of the femur after pathological fracture can occur (8). We report on the third tumor of this type to be described cytogenetically, with a simple translocation involving the long arm of chromosome 7 and the long arm of chromosome 12 presenting as the sole abnormality. The cytogenetic results in our study are different from those of previously published cases (Table 1). In the *Catalog of Chromosome Aberrations in Cancer,* unbalanced

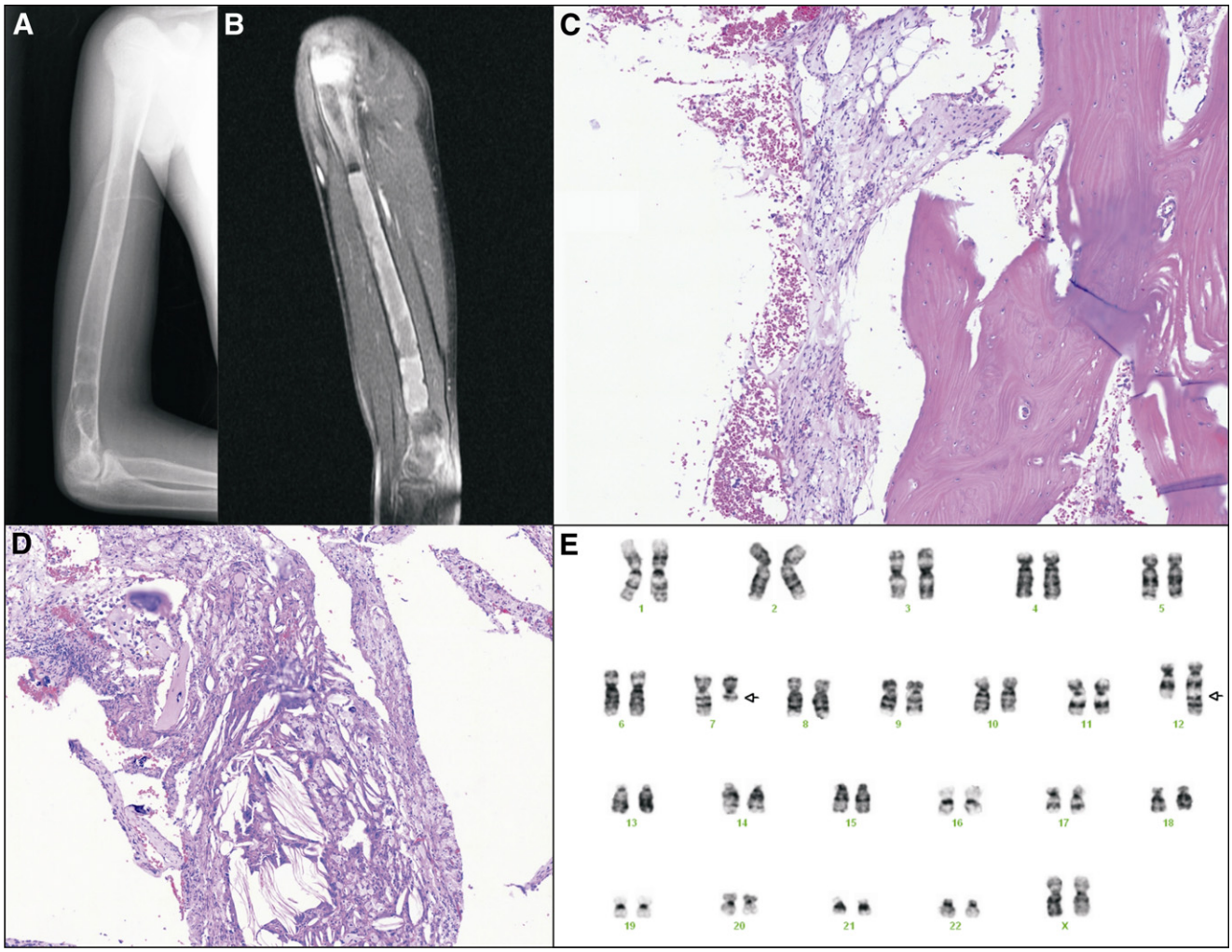

Figure 1 Simple bone cyst. (A) Unicameral cystic lesion affecting the distal two thirds of the left humerus as seen in roentgenography and (B) with limits better defined by magnetic resonance imaging. (C) Cyst wall covered by a thin, loose, connective tissue membrane with an inconspicuous cellular lining and hemorrhagic contents; (D) in some thicker areas, cholesterol crystal clefts, collections of foam histiocytes, and hemosiderin pigment were present. (E) Hematoxylin and eosin, 20×. G-banded karyotype showing the t(7;12)(q21;q24.3).

Table 1 Clinical and cytogenetic data for simple bone cysts

Sex/Age, y	Site	Clonal abnormality	Reference
M/11	Knee	46,XY, der(4),der(6),der(8),der(12),der(12),der(16),der(21)[17]	Vayego et al., 1996
M/9	Femur	46,XY, t(16;20)(p11.2;q13)[4]	Richkind et al., 2002
F/13	Humerus	46,XX, t(7;12)(q21;q24.3)[5]	Current case

structural chromosomal alterations involving 7q21 were detected in two cases of skeletal chondromyxoid fibroma, and unbalanced structural chromosomal alterations involving 12q24.3 were detected in three cases of skeletal osteosarcoma (9). In contrast, there is evidence that autosomal recessive hypophosphatemic rickets 1 is caused by mutations in the *DMP1* gene on chromosome 4q21, and another form of autosomal recessive hypophosphatemic rickets (ARHR2) is caused by mutations in the *ENPP1* gene on chromosome 6q22∼q23 (10). However, rearrangements involving chromosomes 4q21 and 6q22∼q23 were not observed in our patient. The cytogenetic findings described in these lesions are important to the understanding of the molecular mechanisms involved in their development and differentiation from malignant neoplasms, although the clinical behavior rather supports a nonneoplastic nature. Unlike the cytogenetic findings in aneurysmal bone cyst in which the literature data confirm that 16q22 or 17p11∼p13 are nonrandomly involved (11,12), cytogenetic analysis of SBC reveals neither recurrent nor nonrandomly cytogenetic alterations. The number of cytogenetic investigations of bone lesions is extremely limited. Before an association between the present findings and the SBC phenotype may be suggested, further cases must be cytogenetically characterized.

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